Table 1. Median platelet counts at day 1 for cycles 2-6

	No. of patients per cycle/median platelet count at day 1				
	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6
Prechemotherapy and postchemotherapy G-CSF*	16/365 000	12/260 000	9/251 000	4/309 000	2/210 000
Postchemotherapy G-CSF only	18/377 000	17/328 000	15/295 000	12/296 000	10/264 000
P†	.77	.43	.37	‡	‡

*G-CSF = granulocyte colony-stimulating factor.
†Mann–Whitney *U* test.
‡Numbers are too small to calculate the *P* value.

at the double dose of 5 μg/kg twice per day. However, there was no difference in the blood platelet count at day 1 of cycles 2-6 between the two treatment arms, as shown in Table 1 of this correspondence.

Therefore, we have no reason to believe that the adverse effect of prechemotherapy G-CSF is related to a direct adverse effect on platelet count. In our opinion, the more severe thrombocytopenia in patients treated with prechemotherapy G-CSF is caused by an increased proliferation of progenitor cells at the time of administration of the chemotherapy. Possible detrimental effects of prechemotherapy G-CSF on neutrophil recovery may have been masked by the high incidence of severe neutropenia in both study arms as well as a beneficial effect on neutrophil recovery by postchemotherapy G-CSF support. Although not statistically significant, there was a trend of more severe neutropenia in the prechemotherapy G-CSF study arm. The apparent lack of a difference in the development of anemia and red blood cell transfusion requirements may have been caused by the more frequent chemotherapy dose reductions applied in the prechemotherapy G-CSF arm because of the more severe thrombocytopenia.

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Reference

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Notes

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Re: Reversal of Relation Between Body Mass and Endogenous Estrogen Concentrations With Menopausal Status

The risk of breast cancer may be decreased in obese premenopausal women but increased in obese postmenopausal women. Potischman et al. (*1*) recently evaluated the relation of body mass index (BMI, kg/m^2) and hormonal profiles in 88 premenopausal and 210 postmenopausal control subjects from a study of endometrial cancer. They reported a significant decrease in sex hormone-binding globulin (SHBG) concentration as BMI increased in both menopausal groups. As BMI increased, total estradiol increased significantly in postmenopausal women but decreased in premenopausal women, significantly so during the follicular phase. We have repeated these analyses in another dataset.

We used serum hormone concentrations for 182 premenopausal and 178 postmenopausal control subjects from a prospective study of endogenous hormone concentrations and breast cancer on the island of Guernsey, U.K. (*2*). Written informed consent was obtained from all study participants, and procedures were approved by institutional review. Height and weight were measured at interview, a blood sample was collected, and serum was stored at −20 °C. Serum concentrations of SHBG were measured by liquid-phase immunoradiometric assay while estradiol and progesterone were measured by radioimmunoassay. All premenopausal women reported menstruating in their usual pattern and their next menstrual period within 42 days of the interview date. All postmenopausal women reported having had no menstrual periods in the last 12 months. Women were excluded if they were using exogenous sex hormones at the time of blood collection.

Analysis of covariance was used to calculate the geometric mean values within the menopausal groups, and multiple regression was used to test the trend of BMI with hormone concentration. For comparability with the results of Potischman et al., we grouped BMI according to their tertiles. All analyses were adjusted for age and duration of blood storage; analyses involving premenopausal women were also adjusted for day of menstrual cycle (0-2, 3-11, 12-15, 16-21, and 22+ days prior to the next menstrual period for SHBG; 0-2, 3-5, 6-8, 9-11, 12-15, 16-18, 19-21, 22-24, and 25+ days prior to the next menstrual period for estradiol and progesterone). Two-sided *P* values are quoted.

Our results confirm the finding of Potischman et al. that SHBG concentrations decreased as BMI increased in both premenopausal and postmenopausal women and that estradiol concentration increased with BMI in postmenopausal women (Table 1). These relationships have been well established in many previous studies. Potischman et al. reported a 45% lower mean follicular phase estradiol concentration in premenopausal women with high BMI, whereas we found a nonsignificant 20% lower concentration. In serum collected between 0 and 15 days prior to the next menstrual period, we observed a 6% higher mean estradiol concentration and a 12% lower mean progesterone concentration in women with relatively high BMI. Westhoff et al. (*3*) recently reported a 14% higher mean urinary estradiol (P = .16) and an 18% lower mean serum progesterone concentration (P = .003) during the luteal phase in 84 women in the upper half of the distribution of body weight compared with 83 women in the lower half of the distribution.

Severe obesity, associated with an-

Table 1. Geometric mean (95% confidence interval) hormone concentrations by body mass index (BMI) group*

Hormone, U	BMI: Low, <23.2 kg/m²	Middle, 23.2-27.1 kg/m²	High, >27.1 kg/m²	P†
Premenopausal,‡ all cycles				
No. of patients	69	78	35	
SHBG, nmol/L	67.0 (60.8-73.7)	70.3 (64.2-77.0)	44.0 (38.3-50.5)	<.0001
Estradiol, pmol/L	278 (244-318)	310 (274-351)	242 (201-291)	.37
Progesterone, nmol/L	6.90 (5.86-8.14)	7.73 (6.62-9.02)	6.74 (5.35-8.49)	.33
Premenopausal,‡ 16+ days prior to next menstrual period				
No. of patients	40	35	15	
Estradiol, pmol/L	240 (200-289)	251 (206-307)	191 (142-257)	.30
Progesterone, nmol/L	3.08 (2.53-3.75)	3.52 (2.85-4.35)	3.25 (2.36-4.49)	.72
Premenopausal,‡ 0-15 days prior to next menstrual period				
No. of patients	29	43	20	
Estradiol, pmol/L	316 (260-383)	372 (317-436)	335 (243-387)	.92
Progesterone, nmol/L	15.3 (13.3-17.6)	16.9 (13.5-21.1)	13.6 (9.77-18.8)	.09
Postmenopausal§				
No. of patients	50	77	51	
SHBG, nmol/L	75.3 (66.2-85.7)	57.1 (51.6-63.2)	49.6 (43.8-56.2)	<.0001
Estradiol, pmol/L	31.4 (26.9-36.7)	35.8 (31.7-40.5)	49.6 (42.6-57.6)	<.0001

*SHBG = sex hormone-binding globulin.
†Test for linear trend of logarithm of hormone concentration and BMI.
‡Geometric mean adjusted for age, day of menstrual cycle, and duration of blood storage.
§Geometric mean adjusted for age and duration of blood storage.

ovulation, is probably associated with reduced production of both estradiol and progesterone in the second half of the menstrual cycle (*4*). However, in contrast to the unequivocal relationship of BMI with SHBG and with postmenopausal estradiol concentration, any association between BMI and estradiol concentration in premenopausal women with regular menstrual cycles is more subtle.

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Response

Thomas et al. (*1*) have replicated our analysis (*2*) and, in addition, improved the analysis by controlling for day of the cycle. Although not statistically significant, it is interesting that they also found lower estradiol in heavier women, more prominently in the follicular phase. The lack of significance indicates that larger studies would be needed to differentiate a real effect from a chance finding. In addition, the 20% difference in estradiol values in the Guernsey study could be an underestimate, since it seems clear from sex hormone-binding globulin (SHBG) values that the Guernsey women are much lighter than the women in our study, particularly those in the highest body mass index (BMI) category.

As Thomas et al. point out, severe obesity has been associated with increased frequency of anovulation and reduced production of both estradiol and progesterone in the second half of the menstrual cycle. As they indicate, this would not be responsible for the reduced levels seen in both sets of data in follicular phase samples. There are other reasons why it is unlikely to have explained the relationships noted in our own data. Unlike the severely obese women with irregular menses often cited (*3*) to explain the decreased risk of breast cancer with weight, our population-based sample was more likely to be representative of the normal weight distribution of premenopausal women included in studies of breast cancer. With one exception, women in our premenopausal sample reported a menses within 1 month of the interview. Other analyses from the questionnaire indicated that the mean number of days between cycles was similar in heavy and thin women. (Mean number of days between cycles [95% confidence intervals] by BMI tertile: low BMI = 27 [26.5-28.0], middle BMI = 28 [27.4-28.9], and high BMI = 28 days [27.2-28.7].) Furthermore, of the 88 premenopausal women, 10 reported ever having had an interval of 3 or more months between menstrual periods. None of these women were in the highest BMI category (three were in the lowest tertile and seven were in the middle tertile). Therefore, our findings seem relevant to oligomenorrheic women who may reflect the typical heavier women at reduced risk of breast cancer. As noted in our paper, the mechanism we favor is not a decrease in production of estradiol by obese women but rather an increase in its clearance as a result of lowered serum hormone-binding capacity.

We would like to encourage more investigators to attempt to link reproducible hormone values with established breast cancer risk factors to bring long-needed quantification to an area previously noted more for speculation than

Table 1. Comparison of estradiol values (pg/mL) by body mass index (BMI; kg/m^2) tertiles in follicular phase* premenopausal women from two studies (*1*,*2*)

Reference No.	BMI (95% confidence interval) Low	Middle	High	*P*
(*2*)	137 (94-200)	94 (62-142)	76 (47-124)	.03
(*1*)†	65 (54-79)	68 (56-84)	52 (39-70)	.30

*Defined as progesterone ≤50 ng/dL in (*2*) and 16+ days prior to next menstrual period in (*1*).
†Values from Thomas et al. converted from pmol/L to pg/mL for comparison purposes.

data. A comparison of our own data with those from Guernsey also illustrates the substantial methodologic difficulties we must address to move forward in this area. The differences in estradiol values between the two studies for women in the same categories of BMI (Table 1) are greater than some of the differences between categories that we would be interested in detecting. While there may be data-based reasons for some of these differences (as noted for SHBG), we suspect that at least part of the disparity lies in difficulties in laboratory measurement issues. A previous methodologic study (*4*) comparing such steroid measures across several laboratories indicated substantial differences in absolute levels for the same samples, implying real difficulties in comparing results of studies that use different laboratories. As a discipline, we need to address some of these very basic issues if we are going to make advances in delineating hormonal patterns that are determinants of disease.

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